2014-11-15

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World Journal of Gastrointestinal Pathophysiology

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DOI: 10.4291/wjgp.v5.i4.523

World J Gastrointest Pathophysiol 2014 November 15; 5(4): 523-533
ISSN 2150-5330 (online)

REVIEW

Continuing challenges in the diagnosis and management of obscure gastrointestinal bleeding

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Received: January 22, 2014 Revised: July 7, 2014
Accepted: July 17, 2014
Published online: November 15, 2014

Abstract

The diagnosis and management of obscure gastrointestinal bleeding (OGIB) have changed dramatically since the introduction of video capsule endoscopy (VCE) followed by deep enteroscopy and other imaging technologies in the last decade. Significant advances have been made, yet there remains room for improvement in our diagnostic yield and treatment capabilities for recurrent OGIB. In this review, we will summarize the latest technologies for the diagnosis of OGIB, limitations of VCE, technological enhancement in VCE, and different management options for OGIB.

Key words: Obscure gastrointestinal bleeding; Video capsule endoscopy; Deep enteroscopy; Computed tomography enterography; Magnetic resonance enterography

Core tip: Since the advent of capsule endoscopy, significant advances have been made in the imaging of the small bowel that allow for the diagnosis and management of obscure gastrointestinal bleeding. With a decade of knowledge, it is now appropriate for us to look back, critically evaluate our achievements, improve on our current technologies and develop ideas to circumvent some of the shortcomings.

Baptista V, Marya N, Singh A, Rupawala A, Gondal B, Cave D. Continuing challenges in the diagnosis and management of obscure gastrointestinal bleeding. *World J Gastrointest Pathophysiol* 2014; 5(4): 523-533 Available from: URL: http://www.wjgnet.com/2150-5330/full/v5/i4/523.htm DOI: http://dx.doi.org/10.4291/wjgp.v5.i4.523

INTRODUCTION

Remarkable progress has been made since 2001 in the development of technologies that are available to investigate disorders of the small intestine. The wireless video capsule endoscope (VCE) and double balloon enteroscope became available in 2001, followed by the development of computed tomography enterography (CTE) and magnetic resonance enterography (MRE). These tools and newer variations have allowed us to diagnose and manage small bowel lesions in ways that were previously unimaginable. After a 10 year period of remarkable progress it is appropriate to look back, critically evaluate where we are, and use that evaluation as a springboard to critique the technologies and circumvent some of their shortcomings.

Many studies have shown that the diagnostic yield of VCE and deep enteroscopy are similar for obscure gastrointestinal bleeding (OGIB) - approximately in the 40% to 60% range. The higher numbers are for overt obscure bleeding (40% to 92%), occult bleeding (40% to 60%), and iron deficiency (10% to 30%). Assuming indications for these studies are appropriate, a failure-to-diagnose rate of 50% with current techniques appears to be an inconvenient truth. Similarly, recurrent bleeding is distress-

Table 1 Specifications of available capsules

	MiroCam (IntroMedic)	PillCam SB/SB2/SB3 (Given Imaging)	EndoCapsule, EC-10 (Olympus)
Size (mm)	11 × 24	11 × 26	11 × 26
Weight (g)	3.4	3.45	-
Resolution (pixels)	320 × 320	256 × 256	-
Frames per second (fps)	3	2	2
Battery life (h)	11	8-12	8-12
Field of view (°)	150	140/156	145
Communication	Human body communication	Radiofrequency	Radiofrequency
Real time viewer	Yes	Yes	Yes

ingly common. A recent large study from South Korea involving 13 centers and 305 patients showed a detection rate of 51.5%. After VCE only 11.8% received interventional treatment. The overall re-bleeding rate was 19% during the mean of 30 mo[1]. Interestingly the re-bleeding rate was not different between those with positive capsule results and those that had therapy. These observations confirm that we still have a long way to go in terms of better diagnosis and therapy.

DIAGNOSIS OF OGIB

Technology

Various invasive and non-invasive modalities are available for the evaluation of OGIB. These include VCE, deep enteroscopy and a variety of radiological modalities such as CTE, MRE, and conventional and provocative angiography.

Video capsule endoscopy: Currently there are three FDA video capsule endoscopes available in the United States (Table 1). PillCam SB2 (now SB3; Given Imaging, Yoqneam, Israel), EndoCapsule (now EC-10; Olympus, Tokyo, Japan), and MiroCam (IntroMedic, Seoul, South Korea). These capsules are all approximately the same size (11 × 24-26 mm). Most are able to image for up to 12 h, thus reducing the occurrence of incomplete transit. The field of view for all is also similar (140°-156°).

CapsoCam (Capsovision, Saratoga CA, United States) which is in clinical trials in the United States has four cameras allowing for 360° imaging. Unlike traditional capsules that take pictures at a rate of 2-3 frames per second (fps), each of the CapsoCam camera images at the rate of 5 fps for the first two hours and thereafter at 3 fps resulting in 20 and 12 fps respectively. In a prospective comparative study by Pioche *et al*[2], both CapsoCam and PillCam SB2 were found to have similar diagnostic yield (81.8% and 84.8% respectively), however, CapsoCam detected significantly more lesions (108 lesions *vs* 85 lesions), but had a longer reading time (32.0 min *vs* 26.2 min)[2].

MiroCam uses Human Body Communication (HBC) for data transmission which is different from the radiofrequency telemetry of PillCam SB2, SB3 and EndoCapsule. HBC technology uses the human body as a conductive medium for data transmission which expends less electrical power, thereby conferring a longer operating time (12 h) and providing a higher resolution of images (320 × 320 pixels) compared to PillCam SB2 (256 × 256 pixels)[3]. Complete small bowel examination was achieved in 93.3% for MiroCam compared with 84.3% for PillCam SB2. When comparing both capsules for the evaluation of OGIB, the overall concordance was 78.65%, with 77.42% positive agreement and 79.31% negative agreement. MiroCam also has a 42% reduction in missed lesions compared with PillCam[4]. However, the longer recording time along with more image frames captured per second also translate to longer reading time, which may negate the 9% higher rate of small bowel completion and lower missed lesion rate with MiroCam.

Overall, the diagnostic yield of VCE is reported as 38%-92%[5-7]. With the use of VCE in the evaluation and management of OGIB, rebleeding rate was noted to be 15.6% within a 12 mo follow-up period[8]. VCE has the highest yield (92.3%) in those with active overt gastrointestinal (GI) bleeding, and the lowest diagnostic yield (12.9%) in those with a history of obscure GI bleeding[9,10].

Deep enteroscopy: Deep enteroscopy can be performed using double balloon enteroscopy (DBE), single balloon enteroscopy (SBE) or through spiral enteroscopy (SE). These techniques work by pleating the small bowel back over the overtube to minimize looping, thereby allowing the enteroscope to advance forward.

DBE involves two balloons, one each on the distal end of the enteroscope and the overtube. Studies have found the diagnostic yield of DBE is approximately 60%-80% for evaluating OGIB. Success rate of total enteroscopy, with the evaluation of the entire small bowel, either in the antegrade or antegrade plus retrograde fashion, was reported to be 16%-86%[11].

Kamalaporn *et al*[12] looked at detection rates of combined DBE following VCE in OGIB. Overall detection rates for both techniques were similar. Each technique detected lesions not seen by the other, and are complementary in the evaluation of OGIB. VCE is generally performed before DBE, as it can potentially localize the bleeding source and guide the direction of subsequent deep enteroscopy, either in the antegrade or retrograde fashion[13]. In a recent systematic review of over 12000 DBE over a 10 year period, the most common indication for performing DBE (62.5%) was for management of suspected bleeding in the small bowel. DBE was successful in detecting small bowel bleeding in 68.1%[14].

In contrast, SBE involves one balloon. With the use of an angulated enteroscopic tip that can hook onto the small bowel, this technique allows for the enteroscope to advance with a single balloon. Diagnostic yield and intervention rate of SBE were similar to that of DBE (57% *vs* 53% and 32% *vs* 26% respectively)[15], and the procedure

times were both the same at 60 min[16].

SE consists of the Endo-Ease Discovery SB which is a 118 cm long spiral-shaped overtube with spiral ribbing on its surface that is used for enteroscopy *via* the oral route. Diagnostic yield of SE was 57.1%, similar to that of SBE and DBE, and 60% of the angioectasias seen on VCE were detected during SE[17]. Recurrent overt bleeding after SE was 26% during a mean follow up of 2 years[18]. Compared with DBE, SE had both a shorter examination time, along with shorter time to reach the farthest point of examination (43 min *vs* 65 min and 24 min *vs* 43 min respectively). However, DBE allowed for deeper advancement of the enteroscope than SE (310 min *vs* 250 cm)[19].

A recent comparison review noted similar diagnostic yields for SBE, DBE, and SE (53.9%, 64.4%, and 47.0% respectively). Procedure time was fastest in the SE group (oral: 41.0 min, anal: 46 min) followed by SBE (oral: 59.8 min, anal: 68.8 min), and DBE (oral: 71.6 min, anal: 84.5 min). Therapeutic interventions were highest for DBE (40.1%), compared with SBE and SE (26.8% and 29.7%)[20].

CTE and MRE: Similar to VCE, CTE may be used in the evaluation of OGIB to provide a potential road map prior to performing the more invasive DBE. In comparing CTE and VCE, the diagnostic yield for all findings was 34% and 53% respectively. This yield was similar for the detection of neoplastic or mass lesions. However, VCE was superior over CTE in the detection of vascular or inflammatory mucosal lesions. In comparing CTE with DBE, the diagnostic yield was higher for DBE (78% *vs* 38%). Other studies comparing CTE with digital subtraction angiography showed similar yield of 64% and 60% respectively[21].

Agrawal *et al*[22] recently reported that in patients which VCE failed to localize bleeding, CTE may have a utility for the subsequent work up of overt, but not occult or OGIB. The authors found the diagnostic yield to be 50% in overt GI bleed, but 0% in OGIB.

MRE may be considered as an alternative for the initial examination in patients with clinical suspicion of small-bowel stenosis[23] and is also used as a complementary modality for evaluation of patients with small bowel tumors and Crohn's disease.

Angiography: Limited data exists on provocative angiography. In a single center series of patients with obscure and recurrent lower GI bleed, Kim *et al*[24] reported successful definitive treatment of recurrent hemorrhage in 11 of 36 studies (31%) that were performed on 34 patients, with only one complication of ischemic bowel perforation that necessitated bowel resection. There were otherwise no bleeding complications. Leung *et al*[25] compared VCE and angiography for acute overt OGIB and found that the diagnostic yield of VCE was significantly higher than that of angiography (53.3% *vs* 20.0%).

LIMITATIONS OF CAPSULE ENDOSCOPY

Why do we miss lesions?

It has been reported that VCE missed about 11% of all abnormalities in the small bowel. With single mass lesions, the miss rate can be up to 18.9%[26]. Multiple factors account for missed lesions in VCE, including rapid transit through the duodenum and proximal jejunum, unidirectional field of view (about 150°), coupled with a non-axial transit which does not permit the camera to capture the entirety of the mucosal surface. This latter issue explains the discordance of repeat capsule studies in the same patient. Furthermore, inadequate luminal distension and the presence of luminal contents and bubbles further impair complete visualization of the mucosa.

Despite the ability of deep enteroscopes to distend the intestine and wash the mucosa, the diagnostic yield is comparable to that of VCE in most patients when the first deep enteroscopy is attempted from only one direction[12]; achievement of pan enteroscopy is uncommon. The field of view for deep enteroscopes is comparable to VCE, thus it may be difficult to see lesions on the distal aspect of a fold. Anesthesia may also alter hemodynamics of intestinal blood flow in a manner quite different to that of video capsule, and active bleeding originating from a submucosal source is not commonly seen.

Preparation for capsule endoscopy

Capsule image quality plays an important role in the accuracy of capsule interpretation. Presence of food residue, bile, and air bubbles can obscure images. There are currently no guidelines regarding bowel preparation before VCE. Different centers and studies have used various regimens including overnight fasting only for 12 h, clear liquid diet of varying duration, and use of polyethylene glycol (PEG) and/or simethicone. Studies evaluating the role of purgatives/prokinetics as bowel preparation for VCE have been heterogeneous. In a meta-analysis by Song *et al*[27] and the Korean Gut Image Study Group, small bowel visualization quality was found to be enhanced fourfold with use of bowel prep with PEG solution. Two liter (2 L) of PEG solution was similarly effective as 4 L. Diagnostic yield was also slightly improved using PEG solution as compared with overnight fast or clear liquid diet. In another meta-analysis of eight randomized controlled trials comparing use of laxative bowel preparation with fasting alone, PEG based regimens were found to offer better visibility than fasting alone[28]. This is similar to the European Society of gastrointestinal Endoscopy guideline in 2009 recommending purgative bowel preparations that would enhance diagnostic yield of VCE[29]. Use of simethicone with or without bowel prep may also enhance image quality.

Capsule completion rate, however, was not affected with the use of bowel prep, simethicone, or prokinetics. Currently overnight fasting is the standard preparation for VCE in many centers. Alternatively the ASGE recommends 2 L of PEG the evening before the procedure.

Surrounding the controversy regarding use of bowel prep is also the subjective nature of assessing the cleanliness grading system. Current grading systems such as the 10-point quantitative index, or overall assessment of adequacy (adequate or inadequate) are either too cumbersome to calculate or too simplified to be of much utility. With the goal of having an objective assessment, Van Weyenberg *et al*[30] designed a scoring system to assess the quality of bowel preparation with a computed quantitative scale using the color intensities of the tissue color bar. This scoring system, known by the authors as Computed Assessment of Cleansing score is an objective measure, eliminating subjective interpretation by individual readers, and is potentially more reproducible and objective.

Reader error

Recently, a portrayal of physician performance and error in capsule reading was shown in a study by Zheng *et al*[31] to play a big role in missed lesions. In this study, 24 prepared clips of capsule images were read at different modes (single view, duo view, or quad view) and frame speed (15, 20, or 25) by 17 endoscopists, ranging from novice to experienced readers. The detection rates in this study were disappointingly low, ranging from 16% for the detection of blood to 69% for the detection of angioectasias. As expected, ulcers or erosions were more readily detected if they were larger, and masses or polyps were more distinguishable if their color and texture differ from the surrounding mucosa. Abnormal findings appearing in more frames were more likely to be picked up than those appearing in only 1-2 frames. The overall detection rate was also significantly higher when reading in the single view-15 and quad view-20 modes (45% and 47% respectively) compared with reading in single view-25 (26%). This may be explained by the longer dwell time on the screen for each image in quad compared with single view. In another study looking at inter-observer agreement in describing VCE findings, the best agreement was observed in identifying the presence of active bleeding, whereas the worst agreement was in describing size of lesion. Diagnostic concordance was better with angioectasias than for polyps or ulcers/erosions[32].

Missed lesions in the proximal small intestine

Several case reports have noted missed lesions on VCE that were subsequently detected on other imaging modalities such as DBE, CTE or MRE. These lesions were mostly in the proximal small bowel which can be poorly visualized on VCE. This has been evidenced by an earlier study demonstrating that the ampulla of Vater being missed in > 50% of capsule examinations[33]. In a study by Baichi *et al*[34], VCE was performed on 300 consecutive patients presenting with OGIB. Among those patients, 10 small bowel masses were identified, and of those lesions noted, three duodenal masses were missed on previous EGD, with one missed on VCE as well. Further evidence of VCE missing lesions in the proximal small intestine came from a study by Postgate *et al*[35] who reported five tumors missed on VCE for evaluation of OGIB. Three of these tumors were in the distal duodenum, one in the proximal jejunum, and the fifth was a large Peutz-Jegher's polyp in the proximal ileum.

In a study by Selby *et al*[36], capsule endoscopes with varying field of view were evaluated for the ability to identify the ampulla of Vater. The ampulla of Vater was seen in 18% of PillCam SB2 that has a wider field of view (156°) compared to 0% of PillCam (140°). The PillCam SB3 has a variable frame rate of 6 fps when moving fast. It remains to be seen how effective this enhancement will be in visualizing the ampulla of Vater and allowing for better identification of proximal small bowel lesions in the future.

Timing of VCE

The diagnostic yield of VCE for the evaluation of OGIB has been demonstrated to be higher if VCE is performed soon after the onset of bleeding. Of one hundred consecutive patients evaluated for obscure GI bleeding, Pennazio *et al*[9] reported 92.3% positive yield in patients with ongoing overt bleeding (n = 26), 12.9% yield in patients with previous overt bleeding (n = 31) and 44.2% in patients with guaiac positive stools and iron deficiency anemia (n = 43). Similarly, Bresci *et al*[37] reported a positive yield of 91% in patients who underwent VCE within 15 d of obscure GI bleed event versus a yield of 34% in patients who underwent VCE placement after 15 d. Goenka *et al*[38] reported that out of 385 patients investigated for obscure GI bleed, patients with VCE placement within 48 h of overt GI bleed had the highest diagnostic yield (87%). This was significantly greater ($P < 0.05$) compared to patients who had VCE placed after 48 h (68%) of overt GI bleed, as well as those with occult obscure GI bleed (59%).

Recently our group reported that early use of VCE (*i.e.,* within 3 d of hospital admission) led to improved diagnostic yield, higher rate of therapeutic interventions, along with decreased hospital length of stay[39]. In the early deployment group, VCE findings of active bleeding or vascular angioectasia were significantly higher than in the group where VCE was deployed late (after more than 3 d of admission), or in the group where VCE was performed as an outpatient (44.4% *vs* 27.8% *vs* 25.8%). Therapeutic intervention was also carried out more often in the early deployment group compared to the other groups (18.9% *vs* 7.4% for the late group *vs* 10.3% for the outpatient group). Hospital length of stay was also shorter at 6.1 d in the early deployment group, compared with 10.3 d in the late deployment group.

Second look video capsule endoscopy

Several studies have shown that VCE can detect a bleeding site in 45%-66% patients with OGIB, and it is often felt that patients with OGIB and a negative VCE had a low rate of re-bleeding. However, in a study looking at the outcome of 35 patients who had negative VCE for

the evaluation of OGIB, the overall re-bleeding rate was 23% (8 patients) at a median of 15.9 mo of follow up. Four of these patients underwent repeat endoscopy after negative VCE and found previously missed lesions with potential as a bleeding source in the stomach. Overall 13 patients (37%) with or without re-bleeding underwent repeat endoscopy after a negative VCE, which lead to a definitive diagnosis in nine patients (69% who underwent repeat endoscopy). Lesions were located in the stomach and colon in eight of these nine patients[40]. In another study, Vlachogiannakos *et al*[41] noted that in 317 VCE performed for the evaluation of OGIB with negative prior upper endoscopy and colonoscopy, a bleeding source was found on VCE to be outside the small bowel in 3.5% cases, typically duodenum or cecum that was missed by conventional upper endoscopy or colonoscopy. Min *et al*[42] found a higher diagnostic yield for back-to-back VCE and showed that for a single VCE, yield was 37.5%, which increased to 43.8% with a second VCE, and up to 62.5% with back-to-back VCE. Therefore repeat VCE and/or endoscopic evaluations are recommended in cases of severe anemia, or persistent obscure/overt GIB. Timing of VCE is also important as discussed above.

TECHNOLOGICAL ENHANCEMENTS IN CAPSULE ENDOSCOPY

Technological enhancements

Abnormal findings may only be present in a few image frames, and the usefulness of VCE relies on accurate detection of these fleeting images. Several features have been built-in to capsule endoscopy software with the goal of improving detection, such as Suspected Blood Indicator (SBI) and flexible spectral imaging color enhancement (FICE). Different software programs are also equipped with special viewing modes to decrease reading time, such as with QuickView (Given Imaging) and "auto-speed-adjusted" and "express-selected" playback modes (Olympus).

Suspected blood indicator: SBI automatically highlights frames containing several red pixels in an attempt to help capsule reader localize bleeding source. However, use of the SBI is identifying clinically significant lesions is limited by its low sensitivity 56.4% and specificity 33.5%. SBI only has a 24.0% positive predictive value and 67.3% negative predictive value[43]. Intra-luminal bubbles created many of the false positive results. Anecdotally, SBI does have value in overt bleeding where it becomes a solid red bar, the proximal end of which nearly always marks the site of bleeding.

Flexible spectral imaging color enhancement: FICE is an image enhancement system that can obtain bright and high-contrast images. In a study looking at the ability of FICE to detect angioectasia as compared with conventional images, the sensitivity and specificity of detecting angioectasia with FICE images were 91% and 86%, compared with 80% and 100% with conventional mode[44]. FICE reading resulted in more false positive lesions, which can be correctly identified by converting the images to conventional mode.

Quickview system: The QuickView system scans each frame and analyzes patterns/colors to select significant images to create a short video that can then be a quick preview of the entire capsule. Even though QuickView mode may reduce reading time, prospective trials showed a high 8%-12% miss rate[45-47], and it is not recommended as a substitute to reading the entire capsule study.

Auto-speed-adjusted and express-selected playback modes: Olympus capsule endoscopy software systems have equipped an "auto-speed-adjusted" and "express-selected"playback modes. There is also an overview feature which is a one page summary of selected still images which provides the reader with a quick glance of characteristic frames from the capsule study. In the "auto-speed-adjusted" mode, the software speeds up the fps of the video to a maximum of 25 fps when the software detects repeated images similar to the previous frames, thereby potentially reducing the reading time. In the "express-selected" viewing mode, the software skips similar images, and produces a running video stream of only dissimilar images for viewing by the reader. Those skipped images are then gathered into the "expressed-skipped" mode for subsequent viewing if necessary. In a retrospective study of 70 patients to evaluate the clinical efficacy of these functions, Subramanian *et al*[48] noted that the capsule reading time using "express-selected" mode with the overview feature was much lower (19 ± 5 min) than using "auto-speed-adjusted" mode with the overview feature (34 ± 10 min). The missed rate was 8% when the overview function was used alone, but decreased to 0.03% when the overview function was combined with either "express-selected" or "auto-speed-adjusted" playback functions. Though this appears to be promising, further prospective evaluation in a large multicenter trial is needed before this could be recommended for widespread use in clinical practice.

Localization

The clinical problem: While video capsule endoscopy (VCE) is the gold standard for diagnosis of small bowel bleeding, endoscopists are still faced with the clinical challenge of localizing bleeding sources identified by VCE[49,50]. There are many issues at play here. First, the small intestine is a featureless tube which offers only two reliable landmarks for endoscopists - the pylorus and the cecum. Second, the small bowel is stacked upon itself in the peritoneal cavity, meaning that the capsule will traverse through multiple planes as it relates to a single point on the abdominal wall.

Because capsule transit time from the pylorus to the cecum is consistently about four hours, current clinical

practice involves identifying time points associated with the pylorus and cecum and then noting the time point associated with visualization of the bleeding source. Endoscopists can then approximate the distance of the lesion between these two landmarks. One issue with this technique is that if the capsule is not able to visualize the cecum (*e.g.,* because of slow transit time), localization solely based on knowing the time point associated with the pylorus becomes very inaccurate[51,52].

Since the advent of the video capsule, multiple studies have been undertaken to provide a more definitive system of localization. The two major techniques being studied are magnetic field and radiofrequency (RF) localization.

Magnetic field localization: Unlike radiofrequencies, magnetic fields are unaffected by human tissue, allowing for more accurate localization. Magnetic field-based systems also allow the opportunity to control the movement of the capsule while it travels the small bowel using one system[53,54]. Using one system for both capsule control and localization, however, will produce interference that can obstruct both of these functions. Given the accuracy required to control the movements of a capsule through the bowel, this system may not be appropriate. A second issue with magnet-based localization is its application in the clinical setting. Specifically, an examination performed using this system would require a space containing no ferromagnetic materials. Also, magnet-based systems are very complex and would be difficult to utilize in clinics[55].

Radiofrequency localization: An issue surrounding RF-based systems is that radiofrequencies do not easily travel through human tissue. In an effort to better understand the behavior of radiofrequency signals within the human body, a series of multidisciplinary conferences have been convened to address the problems associated with what is called body area networking[56,57]. What is clear is that RF within the body is influenced by multiple factors including tissue densities, juxtaposition of different organs, and other anatomic considerations. Despite this, one advantage of RF-based systems is the ease of utilization in the clinical setting. The first commercially available localization system was the RF-based system attached to the M2A capsule developed by Given Imaging[58]. This localization system has been discontinued due to its inaccuracy. In addition, this system only produces localization data in two dimensions and, therefore, its clinical utility is decreased since capsules travel in multiple planes. Marya *et al*[59] recently reported on a new RF-based localization system developed by Olympus Medical Systems for the new EC-10 capsule. This system has similar accuracy to the Given system while providing three-dimensional localization instead of only two dimensions. The clinical utility of this system cannot be properly assessed until a prospective trial is performed.

Future considerations: Although progress is being made in the development of new localization systems, there are still issues to be addressed. Research needs to be focused on developing a localization system that provides information related to the distance the capsule travels from the pylorus to the suspected bleeding lesion. It is this distance, not simply the three-dimensional location of a capsule within the abdominal cavity, which has the greatest clinical utility to an endoscopist or surgeon in the management of obscure GI bleeding.

MANAGEMENT OF OGIB

Therapeutic options

While progress is being made in the diagnosis of lesions contributing to obscure GI bleeding, the clinical challenge of treating the suspected lesions persists. Traditionally, analysis of particular therapeutic options has been limited to case series or small clinical trials. The decision to choose a particular option is based on several factors. Specifically, clinicians consider where the suspected lesions are within the GI tract, the number of suspected lesions at risk of further bleeding, the degree of bleeding and anemia, co-morbidities and the severity of symptoms experienced by the patient before deciding on a particular therapeutic intervention.

Endoscopic therapy

Once an obscure lesion is localized through endoscopy, the endoscopist has several options available for treatment. Treatments include APC and endoscopic band ligation (EBL).

Argon plasma coagulation: APC therapy is the gold standard therapy for gastric antral vascular ectasias (GAVE) and is widely used to treat angioectasia throughout the GI tract[60-62]. A prospective study by Kwan *et al*[63] provided definitive evidence of the usefulness of APC therapy in 100 patients with both angioectasia and GAVE. In their study the authors found that in a previously transfusion-dependent subset of subjects, over half did not require further transfusions post-APC. In a smaller study population, Herrera *et al*[64] demonstrated a 90% success rate for APC therapy in patients with focal vascular ectasias. In that study, APC was not associated with any adverse effects. Other studies have reported a 2.5% rate of adverse events[65].

Endoscopic band ligation: Historically, EBL has been a treatment for esophageal varices, but its usefulness as a treatment for GAVE and other angioectasia throughout the GI tract is now being realized[66]. In a study of 22 patients, Wells *et al*[67] demonstrated the benefits of EBL, as a subgroup receiving the therapy required fewer treatment sessions and had better-controlled bleeding than those receiving thermal therapy. Earlier studies have shown an equal efficacy and safety profile for EBL in the treatment of Dieulafoy's lesions compared to hemostatic clips or injection therapy[68].

Future directions: Despite important advances in treatments, a large prospective study comparing endoscopic therapies is lacking. As diagnostic measures improve, such a study could prove vital in allowing endoscopists more opportunities to treat obscure GI bleeds.

Pharmacologic therapy

If multiple lesions are suspected to be throughout the GI tract, or if a patient is found to have persistent bleeding despite repeated endoscopic or surgical interventions, pharmacologic therapy should be considered. Pharmacologic therapy may also be pursued for patients with multiple medical co-morbidities that may make them poor candidates for repeated endoscopy or surgical interventions.

Hormonal therapy: The utilization of hormonal therapy (*i.e.,* estrogen plus progesterone) for the treatment of suspected vascular malformations in the GI tract originated from the treatment of hereditary hemorrhagic telangiectasia (HHT, also known as Rendu-Osler-Weber disease). Much of the support for this therapy, however, came only from case reports or from studies with very small sample sizes.

van Cutsem *et al*[69] demonstrated a significant benefit of hormonal therapy compared to placebo (failure rate of therapy 29% compared to 100% for placebo). Despite impressive results, there are many significant issues with this study. Specifically, the sample size of patients was small and the study population included several individuals with HHT who represent a small sub-population of patients with OGIB[69]. These results have been countered by other studies including a larger more recent study from Junquera *et al*[70], which demonstrated no definitive benefit from hormonal therapy compared to the placebo. As other studies suggest, the pathogenesis of vascular malformations in the GI tract is quite different from the process associated with HHT[71,72]. Currently, there is no definitive evidence for the efficacy of hormonal therapy in GI bleeding that is unrelated to HHT.

Anti-angiogenics: The pathogenesis of vascular malformations related to GI bleeding provides multiple options for therapy. In particular, much focus has been placed on the role of vascular endothelial growth factors (VEGF) in the development of these lesions. Junquera *et al*[73] demonstrated that patients with recurrent bleeding secondary to intestinal angiodysplasias (AD) have accumulations of VEGF along the endothelial lining of colonic resection specimens. Research suggests that VEGF becomes overexpressed in oxygen-depleted mucosa, contributing to the formation of AD in older tissues[74,75]. This role of VEGF in the development of AD has created a niche for anti-angiogenic therapy in AD-associated bleeding.

Thalidomide (which has been used in Crohn's disease patients due to its anti-TNF effects) is now being studied in patients with AD-related bleeding. Recently, Ge *et al*[76] performed a randomized controlled trial demonstrating the efficacy of thalidomide in treating AD, 71.4% of patients responded, compared to 3.7% in the control group. Although these results are promising there are significant adverse events associated with thalidomide therapy including leukopenia, deep vein thrombosis, and peripheral neuropathy[77]. Bevacizumab is another anti-angiogenic medication recently studied as a VEGF-inhibitor. Studies have demonstrated its usefulness as an antiangiogenic medication for colon and renal cancer, but there have been no formal studies performed in patients with recurrent GI bleeding from suspected vascular malformations[78].

Somatostatin analogues: The most well-studied somatostatin analogue for the treatment of OGIB is octreotide. The suspected mechanism of action is the ability to inhibit the production of intestinal enzymes (*e.g.,* cholecystokinin, gastrin, and vasointestinal peptide), decrease splanchnic blood flow, decrease platelet aggregation, and decrease angiogenesis. One case series by Nardone *et al*[79], demonstrated that octreotide treatment stopped bleeding in 10 of 17 patients. The authors noted that patients receiving octreotide therapy experienced few side effects. The most common side effects of octreotide therapy are abdominal discomfort and diarrhea, considered to be relatively mild compared to side effects of some of the other therapies listed here[80].

Future directions: While the pathogenesis of AD-related bleeding offers multiple promising opportunities for intervention, a focus on developing randomized-controlled trials to better assess these therapies is needed to define their clinical utility and potential side effects.

Surgical therapy

With advances in endoscopic techniques that allow for visualization and treatment of lesions responsible for OGIB, surgery has become less of a necessity. Now, surgery may be pursued in patients who have failed medical and endoscopic therapy, as well as patients who present with an acute hemorrhage. But in all cases a target lesion needs to be defined preoperatively to avoid the high likelihood of a negative exploration. Research in this field has focused on the localization of lesions to allow surgeons the opportunity to make a curative resection. Studies have demonstrated the benefits of injecting methylene blue dye as an intraoperative technique to allow surgeons to identify the areas of the bowel affected by AD[81,82]. Although this technique has been used since 1978, recent studies have suggested adaptations to make the process easier. For example, D'Mello *et al*[83] presented a case report using digital subtraction angiography to reveal a vascular malformation which they then accessed easily using a microcatheter. Further investigation into capsule endoscopy localization and intraoperative localization of lesions will allow surgeons to make more definitive resections while decreasing the length of bowel needed to be removed.

RECURRENCE OF OGIB

One of the biggest challenges associated with OGIB is that of recurrence. The rate of re-bleeding varies in literature depending on center, duration of follow up and cause of bleeding. Studies have demonstrated the re-bleeding rate to be in the range of 40%-60% when associated with a finding of angiodysplasia on VCE[84,85]. Endo *et al*[86] studied the rate of re-bleeding after intervention for lesions detected on VCE, and found 50% re-bleeding rate in patients with angiodysplasia despite endoscopic intervention. The re-bleeding rate was also higher for patients with clinically insignificant lesions, regardless of whether endoscopic intervention was performed[86]. Patients requiring multiple transfusions for recurrent bleeding typically have multiple co-morbidities, such as chronic renal failure or use of anticoagulation, that are also independent risks for re-bleeding. Patients with recurrent bleeding require multiple endoscopic procedures and are thus at increased risk of complications from these procedures.

Another challenge associated with recurrent OGIB is negative endoscopic findings on VCE or deep enteroscopy. Evidence is conflicting in this area with some studies showing a higher rate of bleeding with normal mucosa or insignificant lesions on endoscopy[84], whereas others show higher rate of recurrent bleeding associated with positive findings on VCE[85]. Studies have reported re-bleeding rate as low as 5.6% and 11% in patients with negative VCE[85,87]. Koh *et al*[88] investigated long-term outcome in OGIB after negative VCE, and found that the overall re-bleeding rate was 28.4%. The re-bleeding rate was higher in patients with positive VCE (36.8%) than in those with negative findings (22.8%)[88]. It is also reported that in VCE-directed interventions, 50%-66% of patients remain transfusion-free without recurrent bleeding[89,90].

FUTURE IN THE DIAGNOSIS AND MANAGEMENT OF OGIB

Advances in capsule endoscopy have included longer battery life, higher image capture frame rate, wider angle of view, improved image resolution, along with enhanced software features to assist in reading. Studies suggest that there is room for further education in reading VCE videos. The more widespread use of early capsule deployment in overt OGIB should enhance diagnostic yields and increase therapeutic intervention rates. The ability to define distance travelled by the capsule would be very helpful in lesion localization. The new 3-D localization software is a step in the right direction. Difficult to detect sources of bleeding may be better controlled by medical means and should stimulate drug development and clinical trials of such agents. The tools for deep enteroscopy are likely to evolve shortly. However, cost constraints for these procedures would preclude their primary deployment in most parts of the world. Thus VCE and DE are likely to remain complimentary procedures for the foreseeable future.

REFERENCES

1 **Min YW**, Kim JS, Jeon SW, Jeen YT, Im JP, Cheung DY, Choi MG, Kim JO, Lee KJ, Ye BD, Shim KN, Moon JS, Kim JH, Hong SP, Chang DK. Long-term outcome of capsule endoscopy in obscure gastrointestinal bleeding: a nationwide analysis. *Endoscopy* 2014; **46**: 59-65 [PMID: 24254387 DOI: 10.1055/s-0033-1358803]

2 **Pioche M**, Vanbiervliet G, Jacob P, Duburque C, Gincul R, Filoche B, Daudet J, Filippi J, Saurin JC. Prospective randomized comparison between axial- and lateral-viewing capsule endoscopy systems in patients with obscure digestive bleeding. *Endoscopy* 2014; **46**: 479-484 [PMID: 24285122 DOI: 10.1055/s-0033-1358832]

3 **Bang S**, Park JY, Jeong S, Kim YH, Shim HB, Kim TS, Lee DH, Song SY. First clinical trial of the "MiRo" capsule endoscope by using a novel transmission technology: electric-field propagation. *Gastrointest Endosc* 2009; **69**: 253-259 [PMID: 18640676 DOI: 10.1016/j.gie.2008.04.033]

4 **Choi EH**, Mergener K, Semrad C, Fisher L, Cave DR, Dodig M, Burke C, Leighton JA, Kastenberg D, Simpson P, Sul J, Bhattacharya K, Charles R, Gerson L, Weber L, Eisen G, Reidel W, Vargo JJ, Wakim-Fleming J, Lo SK. A multicenter, prospective, randomized comparison of a novel signal transmission capsule endoscope to an existing capsule endoscope. *Gastrointest Endosc* 2013; **78**: 325-332 [PMID: 23664161 DOI: 10.1016/j.gie.2013.02.039]

5 **Fireman Z**, Friedman S. Diagnostic yield of capsule endoscopy in obscure gastrointestinal bleeding. *Digestion* 2004; **70**: 201-206 [PMID: 15627766 DOI: 10.1159/000082834]

6 **Saurin JC**, Delvaux M, Gaudin JL, Fassler I, Villarejo J, Vahedi K, Bitoun A, Canard JM, Souquet JC, Ponchon T, Florent C, Gay G. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. *Endoscopy* 2003; **35**: 576-584 [PMID: 12822092 DOI: 10.1055/s-2003-40244]

7 **Rondonotti E**, Villa F, Mulder CJ, Jacobs MA, de Franchis R. Small bowel capsule endoscopy in 2007: indications, risks and limitations. *World J Gastroenterol* 2007; **13**: 6140-6149 [PMID: 18069752 DOI: 10.3748/wjg.13.6140]

8 **Apostolopoulos P**, Liatsos C, Gralnek IM, Kalantzis C, Giannakoulopoulou E, Alexandrakis G, Tsibouris P, Kalafatis E, Kalantzis N. Evaluation of capsule endoscopy in active, mild-to-moderate, overt, obscure GI bleeding. *Gastrointest Endosc* 2007; **66**: 1174-1181 [PMID: 18061718 DOI: 10.1016/j.gie.2007.06.058]

9 **Pennazio M**, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, De Franchis R. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. *Gastroenterology* 2004; **126**: 643-653 [PMID: 14988816 DOI: 10.1053/j.gastro.2003.11.057]

10 **Singh A**, Baptista V, Stoicov C, Cave DR. Evaluation of small bowel bleeding. *Curr Opin Gastroenterol* 2013; **29**: 119-124 [PMID: 23168835 DOI: 10.1097/MOG.0b013e32835bdc1a]

11 **Leighton JA**. The role of endoscopic imaging of the small bowel in clinical practice. *Am J Gastroenterol* 2011; **106**: 27-36; quiz 37 [PMID: 20978483 DOI: 10.1038/ajg.2010.410]

12 **Kamalaporn P**, Cho S, Basset N, Cirocco M, May G, Kortan P, Kandel G, Marcon N. Double-balloon enteroscopy following capsule endoscopy in the management of obscure gastrointestinal bleeding: outcome of a combined approach. *Can J Gastroenterol* 2008; **22**: 491-495 [PMID: 18478135]

13 **Shishido T**, Oka S, Tanaka S, Aoyama T, Watari I, Imagawa H, Yoshida S, Chayama K. Diagnostic yield of capsule endoscopy vs. double-balloon endoscopy for patients who have undergone total enteroscopy with obscure gastrointes-

tinal bleeding. *Hepatogastroenterology* 2012; **59**: 955-959 [PMID: 22580642 DOI: 10.5754/hge12242]
14 **Xin L**, Liao Z, Jiang YP, Li ZS. Indications, detectability, positive findings, total enteroscopy, and complications of diagnostic double-balloon endoscopy: a systematic review of data over the first decade of use. *Gastrointest Endosc* 2011; **74**: 563-570 [PMID: 21620401 DOI: 10.1016/j.gie.2011.03.1239]
15 **Teshima CW**. Small bowel endoscopy for obscure GI bleeding. *Best Pract Res Clin Gastroenterol* 2012; **26**: 247-261 [PMID: 22704568 DOI: 10.1016/j.bpg.2012.01.020]
16 **Efthymiou M**, Desmond PV, Brown G, La Nauze R, Kaffes A, Chua TJ, Taylor AC. SINGLE-01: a randomized, controlled trial comparing the efficacy and depth of insertion of single- and double-balloon enteroscopy by using a novel method to determine insertion depth. *Gastrointest Endosc* 2012; **76**: 972-980 [PMID: 22980289 DOI: 10.1016/j.gie.2012.06.033]
17 **Buscaglia JM**, Richards R, Wilkinson MN, Judah JR, Lam Y, Nagula S, Draganov PV. Diagnostic yield of spiral enteroscopy when performed for the evaluation of abnormal capsule endoscopy findings. *J Clin Gastroenterol* 2011; **45**: 342-346 [PMID: 20861800 DOI: 10.1097/MCG.0b013e3181eeb74b]
18 **Williamson JB**, Judah JR, Gaidos JK, Collins DP, Wagh MS, Chauhan SS, Zoeb S, Buscaglia JM, Yan H, Hou W, Draganov PV. Prospective evaluation of the long-term outcomes after deep small-bowel spiral enteroscopy in patients with obscure GI bleeding. *Gastrointest Endosc* 2012; **76**: 771-778 [PMID: 22771101 DOI: 10.1016/j.gie.2012.05.025]
19 **May A**, Manner H, Aschmoneit I, Ell C. Prospective, crossover, single-center trial comparing oral double-balloon enteroscopy and oral spiral enteroscopy in patients with suspected small-bowel vascular malformations. *Endoscopy* 2011; **43**: 477-483 [PMID: 21437852 DOI: 10.1055/s-0030-1256340]
20 **Lenz P**, Domagk D. Double- vs. single-balloon vs. spiral enteroscopy. *Best Pract Res Clin Gastroenterol* 2012; **26**: 303-313 [PMID: 22704572 DOI: 10.1016/j.bpg.2012.01.021]
21 **Wang Z**, Chen JQ, Liu JL, Qin XG, Huang Y. CT enterography in obscure gastrointestinal bleeding: a systematic review and meta-analysis. *J Med Imaging Radiat Oncol* 2013; **57**: 263-273 [PMID: 23721134 DOI: 10.1111/1754-9485.12035]
22 **Agrawal JR**, Travis AC, Mortele KJ, Silverman SG, Maurer R, Reddy SI, Saltzman JR. Diagnostic yield of dual-phase computed tomography enterography in patients with obscure gastrointestinal bleeding and a non-diagnostic capsule endoscopy. *J Gastroenterol Hepatol* 2012; **27**: 751-759 [PMID: 22098076 DOI: 10.1111/j.1440-1746.2011.06959.x]
23 **Wiarda BM**, Heine DG, Mensink P, Stolk M, Dees J, Hazenberg HJ, Stoker J, Kuipers EJ. Comparison of magnetic resonance enteroclysis and capsule endoscopy with balloon-assisted enteroscopy in patients with obscure gastrointestinal bleeding. *Endoscopy* 2012; **44**: 668-673 [PMID: 22528671]
24 **Kim CY**, Suhocki PV, Miller MJ, Khan M, Janus G, Smith TP. Provocative mesenteric angiography for lower gastrointestinal hemorrhage: results from a single-institution study. *J Vasc Interv Radiol* 2010; **21**: 477-483 [PMID: 20171902 DOI: 10.1055/s-0032-1309386]
25 **Leung WK**, Ho SS, Suen BY, Lai LH, Yu S, Ng EK, Ng SS, Chiu PW, Sung JJ, Chan FK, Lau JY. Capsule endoscopy or angiography in patients with acute overt obscure gastrointestinal bleeding: a prospective randomized study with long-term follow-up. *Am J Gastroenterol* 2012; **107**: 1370-1376 [PMID: 22825363 DOI: 10.1038/ajg.2012.212]
26 **Lewis BS**, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy* 2005; **37**: 960-965 [PMID: 16189768 DOI: 10.1055/s-2005-870353]
27 **Song HJ**, Moon JS, Do JH, Cha IH, Yang CH, Choi MG, Jeen YT, Kim HJ. Guidelines for Bowel Preparation before Video Capsule Endoscopy. *Clin Endosc* 2013; **46**: 147-154 [PMID: 23614124 DOI: 10.5946/ce.2013.46.2.147]
28 **Belsey J**, Crosta C, Epstein O, Fischbach W, Layer P, Parente F, Halphen M. Meta-analysis: efficacy of small bowel preparation for small bowel video capsule endoscopy. *Curr Med Res Opin* 2012; **28**: 1883-1890 [PMID: 23136911 DOI: 10.1185/03007995.2012.747953]
29 **Ladas SD**, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; **42**: 220-227 [PMID: 20195992 DOI: 10.1055/s-0029-1243968]
30 **Van Weyenberg SJ**, De Leest HT, Mulder CJ. Description of a novel grading system to assess the quality of bowel preparation in video capsule endoscopy. *Endoscopy* 2011; **43**: 406-411 [PMID: 21425039]
31 **Zheng Y**, Hawkins L, Wolff J, Goloubeva O, Goldberg E. Detection of lesions during capsule endoscopy: physician performance is disappointing. *Am J Gastroenterol* 2012; **107**: 554-560 [PMID: 22233695 DOI: 10.1055/s-0030-1256228]
32 **Pezzoli A**, Cannizzaro R, Pennazio M, Rondonotti E, Zancanella L, Fusetti N, Simoni M, Cantoni F, Melina R, Alberani A, Caravelli G, Villa F, Chilovi F, Casetti T, Iaquinto G, D'imperio N, Gullini S. Interobserver agreement in describing video capsule endoscopy findings: a multicentre prospective study. *Dig Liver Dis* 2011; **43**: 126-131 [PMID: 20817579 DOI: 10.1016/j.dld.2010.07.007]
33 **Kong H**, Kim YS, Hyun JJ, Cho YJ, Keum B, Jeen YT, Lee HS, Chun HJ, Um SH, Lee SW, Choi JH, Kim CD, Ryu HS, Hyun JH. Limited ability of capsule endoscopy to detect normally positioned duodenal papilla. *Gastrointest Endosc* 2006; **64**: 538-541 [PMID: 16996345 DOI: 10.1016/j.gie.2006.02.028]
34 **Baichi MM**, Arifuddin RM, Mantry PS. Small-bowel masses found and missed on capsule endoscopy for obscure bleeding. *Scand J Gastroenterol* 2007; **42**: 1127-1132 [PMID: 17710681 DOI: 10.1080/00365520701266898]
35 **Postgate A**, Despott E, Burling D, Gupta A, Phillips R, O'Beirne J, Patch D, Fraser C. Significant small-bowel lesions detected by alternative diagnostic modalities after negative capsule endoscopy. *Gastrointest Endosc* 2008; **68**: 1209-1214 [PMID: 19028234 DOI: 10.1016/j.gie.2008.06.035]
36 **Selby WS**, Prakoso E. The inability to visualize the ampulla of Vater is an inherent limitation of capsule endoscopy. *Eur J Gastroenterol Hepatol* 2011; **23**: 101-103 [PMID: 21030868 DOI: 10.1097/MEG.0b013e3283410210]
37 **Bresci G**, Parisi G, Bertoni M, Tumino E, Capria A. The role of video capsule endoscopy for evaluating obscure gastrointestinal bleeding: usefulness of early use. *J Gastroenterol* 2005; **40**: 256-259 [PMID: 15830284 DOI: 10.1007/s00535-004-1532-5]
38 **Goenka MK**, Majumder S, Kumar S, Sethy PK, Goenka U. Single center experience of capsule endoscopy in patients with obscure gastrointestinal bleeding. *World J Gastroenterol* 2011; **17**: 774-778 [PMID: 21390148 DOI: 10.3748/wjg.v17.i6.774]
39 **Singh A**, Marshall C, Chaudhuri B, Okoli C, Foley A, Person SD, Bhattacharya K, Cave DR. Timing of video capsule endoscopy relative to overt obscure GI bleeding: implications from a retrospective study. *Gastrointest Endosc* 2013; **77**: 761-766 [PMID: 23375526 DOI: 10.1016/j.gie.2012.11.041]
40 **Lorenceau-Savale C**, Ben-Soussan E, Ramirez S, Antonietti M, Lerebours E, Ducrotté P. Outcome of patients with obscure gastrointestinal bleeding after negative capsule endoscopy: results of a one-year follow-up study. *Gastroenterol Clin Biol* 2010; **34**: 606-611 [PMID: 20822872]
41 **Vlachogiannakos J**, Papaxoinis K, Viazis N, Kegioglou A, Binas I, Karamanolis D, Ladas SD. Bleeding lesions within reach of conventional endoscopy in capsule endoscopy examinations for obscure gastrointestinal bleeding: is repeating endoscopy economically feasible? *Dig Dis Sci* 2011; **56**: 1763-1768 [PMID: 21302137 DOI: 10.1016/j.gcb.2010.06.009]
42 **Min BH**, Chang DK, Kim BJ, Lee IS, Choi MG. Does Back-

To-Back Capsule Endoscopy Increase the Diagnostic Yield over a Single Examination in Patients with Obscure Gastrointestinal Bleeding? *Gut Liver* 2010; **4**: 54-59 [PMID: 20479913 DOI: 10.5009/gnl.2010.4.1.54]

43 **D'Halluin PN**, Delvaux M, Lapalus MG, Sacher-Huvelin S, Ben Soussan E, Heyries L, Filoche B, Saurin JC, Gay G, Heresbach D. Does the "Suspected Blood Indicator" improve the detection of bleeding lesions by capsule endoscopy? *Gastrointest Endosc* 2005; **61**: 243-249 [PMID: 15729233 DOI: 10.1016/S0016-5107(04)02587-8]

44 **Nakamura M**, Ohmiya N, Miyahara R, Ando T, Watanabe O, Kawashima H, Itoh A, Hirooka Y, Goto H. Usefulness of flexible spectral imaging color enhancement (FICE) for the detection of angiodysplasia in the preview of capsule endoscopy. *Hepatogastroenterology* 2012; **59**: 1474-1477 [PMID: 22683964 DOI: 10.5754/hge10747]

45 **Shiotani A**, Honda K, Kawakami M, Murao T, Matsumoto H, Tarumi K, Kusunoki H, Hata J, Haruma K. Evaluation of RAPID(®) 5 Access software for examination of capsule endoscopies and reading of the capsule by an endoscopy nurse. *J Gastroenterol* 2011; **46**: 138-142 [PMID: 20821237 DOI: 10.1007/s00535-010-0312-7]

46 **Westerhof J**, Koornstra JJ, Weersma RK. Can we reduce capsule endoscopy reading times? *Gastrointest Endosc* 2009; **69**: 497-502 [PMID: 19012887 DOI: 10.1016/j.gie.2008.05.070]

47 **Kyriakos N**, Karagiannis S, Galanis P, Liatsos C, Zouboulis-Vafiadis I, Georgiou E, Mavrogiannis C. Evaluation of four time-saving methods of reading capsule endoscopy videos. *Eur J Gastroenterol Hepatol* 2012; **24**: 1276-1280 [PMID: 22825645 DOI: 10.1097/MEG.0b013e32835718d2]

48 **Subramanian V**, Mannath J, Telakis E, Ragunath K, Hawkey CJ. Efficacy of new playback functions at reducing small-bowel wireless capsule endoscopy reading times. *Dig Dis Sci* 2012; **57**: 1624-1628 [PMID: 22327240 DOI: 10.1007/s10620-012-2074-y]

49 **Ginsberg GG**, Barkun AN, Bosco JJ, Isenberg GA, Nguyen CC, Petersen BT, Silverman WB, Slivka A, Taitelbaum G. Wireless capsule endoscopy: August 2002. *Gastrointest Endosc* 2002; **56**: 621-624 [PMID: 12397265]

50 **Iddan G**, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. *Nature* 2000; **405**: 417 [PMID: 10839527 DOI: 10.1038/35013140]

51 **Moglia A**, Menciassi A, Dario P, Cuschieri A. Capsule endoscopy: progress update and challenges ahead. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 353-362 [PMID: 19434097 DOI: 10.1038/nrgastro.2009.69]

52 **Wang X**, Meng M. Perspective of active capsule endoscope: actuation and localization. *Int J Mechatron Autom* 2011; **1**: 38-45 [DOI: 10.1504/IJMA.2011.039154]

53 **Hu C**, -H Meng M, Mandal M. Efficient linear algorithm for magnetic localization and orientation in capsule endoscopy. *Conf Proc IEEE Eng Med Biol Soc* 2005; **7**: 7143-7146 [PMID: 17281923 DOI: 10.1109/IEMBS.2005.1616154]

54 **Wang X**, Meng MQ, Hu C. A localization method using 3-axis magnetoresistive sensors for tracking of capsule endoscope. *Conf Proc IEEE Eng Med Biol Soc* 2006; **1**: 2522-2525 [PMID: 17946518 DOI: 10.1109/IEMBS.2006.260711]

55 **Than TD**, Alici G, Zhou H, Li W. A review of localization systems for robotic endoscopic capsules. *IEEE Trans Biomed Eng* 2012; **59**: 2387-2399 [PMID: 22736628 DOI: 10.1109/TBME.2012.2201715]

56 **Pahlavan K**, Rao G, Ye Y, Makarov S, Khan U, Swar P, Cave D, Karellas A, Krishnamurthy P, Sayrafian K. RF Localization for Wireless Capsule Endoscopy. *Int J Wirel Inf Netw* 2012; **19**: 326-340 [DOI: 10.1007/s10776-012-0195-z]

57 **Pahlavan K**, Ye Y, Fu R, Khan U. Challenges in channel measurement and modeling for RF localization inside the human body. *Int J Embed Real-time Commun Syst* 2012; **3**: 18-37 [DOI: 10.4018/jertcs.2012070102]

58 **Fischer D**, Schreiber R, Levi D, Eliakim R. Capsule endoscopy: the localization system. *Gastrointest Endosc Clin N Am* 2004; **14**: 25-31 [PMID: 15062377 DOI: 10.1016/j.giec.2003.10.020]

59 **Marya N**, Karellas A, Foley A, Roychowdhury A, Cave D. Computerized 3-dimensional localization of a video capsule in the abdominal cavity: validation by digital radiography. *Gastrointest Endosc* 2014; **79**: 669-674 [PMID: 24424401 DOI: 10.1016/j.gie.2013.11.022]

60 **Fuccio L**, Zagari RM, Serrani M, Eusebi LH, Grilli D, Cennamo V, Laterza L, Asioli S, Ceroni L, Bazzoli F. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia-related bleeding in patients with liver cirrhosis. *Digestion* 2009; **79**: 143-150 [PMID: 19329853 DOI: 10.1159/000210087]

61 **Lecleire S**, Ben-Soussan E, Antonietti M, Goria O, Riachi G, Lerebours E, Ducrotté P. Bleeding gastric vascular ectasia treated by argon plasma coagulation: a comparison between patients with and without cirrhosis. *Gastrointest Endosc* 2008; **67**: 219-225 [PMID: 18226684 DOI: 10.1016/j.gie.2007]

62 **Sebastian S**, McLoughlin R, Qasim A, O'Morain CA, Buckley MJ. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia (watermelon stomach): long-term results. *Dig Liver Dis* 2004; **36**: 212-217 [PMID: 15046192 DOI: 10.1016/j.dld.2003.11.028]

63 **Kwan V**, Bourke MJ, Williams SJ, Gillespie PE, Murray MA, Kaffes AJ, Henriquez MS, Chan RO. Argon plasma coagulation in the management of symptomatic gastrointestinal vascular lesions: experience in 100 consecutive patients with long-term follow-up. *Am J Gastroenterol* 2006; **101**: 58-63 [PMID: 16405534 DOI: 10.1111/j.1572-0241.2006.00370.x]

64 **Herrera S**, Bordas JM, Llach J, Ginès A, Pellisé M, Fernández-Esparrach G, Mondelo F, Mata A, Cárdenas A, Castells A. The beneficial effects of argon plasma coagulation in the management of different types of gastric vascular ectasia lesions in patients admitted for GI hemorrhage. *Gastrointest Endosc* 2008; **68**: 440-446 [PMID: 18423466 DOI: 10.1016/j.gie.2008.02.009]

65 **Canard JM**, Védrenne B. Clinical application of argon plasma coagulation in gastrointestinal endoscopy: has the time come to replace the laser? *Endoscopy* 2001; **33**: 353-357 [PMID: 11315899 DOI: 10.1055/s-2001-13686]

66 **Park CH**, Joo YE, Kim HS, Choi SK, Rew JS, Kim SJ. A prospective, randomized trial of endoscopic band ligation versus endoscopic hemoclip placement for bleeding gastric Dieulafoy's lesions. *Endoscopy* 2004; **36**: 677-681 [PMID: 15280971 DOI: 10.1055/s-2004-825661]

67 **Wells CD**, Harrison ME, Gurudu SR, Crowell MD, Byrne TJ, Depetris G, Sharma VK. Treatment of gastric antral vascular ectasia (watermelon stomach) with endoscopic band ligation. *Gastrointest Endosc* 2008; **68**: 231-236 [PMID: 18533150 DOI: 10.1016/j.gie.2008.02.021]

68 **Mumtaz R**, Shaukat M, Ramirez FC. Outcomes of endoscopic treatment of gastroduodenal Dieulafoy's lesion with rubber band ligation and thermal/injection therapy. *J Clin Gastroenterol* 2003; **36**: 310-314 [PMID: 12642736 DOI: 10.1097/00004836-200304000-00006]

69 **van Cutsem E**, Rutgeerts P, Vantrappen G. Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. *Lancet* 1990; **335**: 953-955 [PMID: 1970032 DOI: 10.1016/0140-6736(90)91010-8]

70 **Junquera F**, Feu F, Papo M, Videla S, Armengol JR, Bordas JM, Saperas E, Piqué JM, Malagelada JR. A multicenter, randomized, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. *Gastroenterology* 2001; **121**: 1073-1079 [PMID: 11677198 DOI: 10.1053/gast.2001.28650]

71 **McAllister KA**, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic tel-

angiectasia type 1. *Nat Genet* 1994; **8**: 345-351 [PMID: 7894484 DOI: 10.1038/ng1294-345]
72 **Sami SS**, Al-Araji SA, Ragunath K. Review article: gastrointestinal angiodysplasia - pathogenesis, diagnosis and management. *Aliment Pharmacol Ther* 2014; **39**: 15-34 [PMID: 24138285 DOI: 10.1111/apt.12527]
73 **Junquera F**, Saperas E, de Torres I, Vidal MT, Malagelada JR. Increased expression of angiogenic factors in human colonic angiodysplasia. *Am J Gastroenterol* 1999; **94**: 1070-1076 [PMID: 10201485 DOI: 10.1111/j.1572-0241.1999.01017.x]
74 **Shweiki D**, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 1992; **359**: 843-845 [PMID: 1279431 DOI: 10.1038/359843a0]
75 **Stavri GT**, Zachary IC, Baskerville PA, Martin JF, Erusalimsky JD. Basic fibroblast growth factor upregulates the expression of vascular endothelial growth factor in vascular smooth muscle cells. Synergistic interaction with hypoxia. *Circulation* 1995; **92**: 11-14 [PMID: 7788904 DOI: 10.1161/01.CIR.92.1.11]
76 **Ge ZZ**, Chen HM, Gao YJ, Liu WZ, Xu CH, Tan HH, Chen HY, Wei W, Fang JY, Xiao SD. Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. *Gastroenterology* 2011; **141**: 1629-1637.e1-4 [PMID: 21784047 DOI: 10.1053/j.gastro.2011.07.018]
77 **Szilagyi A**, Ghali MP. Pharmacological therapy of vascular malformations of the gastrointestinal tract. *Can J Gastroenterol* 2006; **20**: 171-178 [PMID: 16550261]
78 **Bauditz J**, Lochs H. Angiogenesis and vascular malformations: antiangiogenic drugs for treatment of gastrointestinal bleeding. *World J Gastroenterol* 2007; **13**: 5979-5984 [PMID: 18023086 DOI: 10.3748/wjg.13.5979]
79 **Nardone G**, Rocco A, Balzano T, Budillon G. The efficacy of octreotide therapy in chronic bleeding due to vascular abnormalities of the gastrointestinal tract. *Aliment Pharmacol Ther* 1999; **13**: 1429-1436 [PMID: 10571598 DOI: 10.1046/j.1365-2036.1999.00647.x]
80 **Brown C**, Subramanian V, Wilcox CM, Peter S. Somatostatin analogues in the treatment of recurrent bleeding from gastrointestinal vascular malformations: an overview and systematic review of prospective observational studies. *Dig Dis Sci* 2010; **55**: 2129-2134 [PMID: 20393879 DOI: 10.1007/s10620-010-1193-6]
81 **Schechter S**, Deorchis D, Bass J, Marcoux DA. Angiographic selective methylene blue staining of an occult small-bowel arteriovenous malformation. *Am Surg* 2002; **68**: 15-17 [PMID: 12467310]
82 **Schrodt JF**, Bradford WR. Presurgical angiographic localization of small bowel bleeding site with methylene blue injection. *J Ky Med Assoc* 1996; **94**: 192-195 [PMID: 8935401]
83 **D'Mello A**, Sawant AD, Kulkarni A, Joshi A, Shah SR. Methylene blue dye injection for identification of occult gastrointestinal bleeding. *Indian J Gastroenterol* 2014; **33**: 85-86 [PMID: 23990392 DOI: 10.1007/s12664-013-0380-8]
84 **Gerson LB**, Batenic MA, Newsom SL, Ross A, Semrad CE. Long-term outcomes after double-balloon enteroscopy for obscure gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2009; **7**: 664-669 [PMID: 19514115 DOI: 10.1016/j.cgh.2009.01.021]
85 **Lai LH**, Wong GL, Chow DK, Lau JY, Sung JJ, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *Am J Gastroenterol* 2006; **101**: 1224-1228 [PMID: 16771942 DOI: 10.1111/j.1572-0241.2006.00565.x]
86 **Endo H**, Matsuhashi N, Inamori M, Akimoto K, Ohya T, Yanagawa T, Asayama M, Hisatomi K, Teratani T, Fujita K, Yoneda M, Nakajima A. Rebleeding rate after interventional therapy directed by capsule endoscopy in patients with obscure gastrointestinal bleeding. *BMC Gastroenterol* 2008; **8**: 12 [PMID: 18430253 DOI: 10.1186/1471-230X-8-12]
87 **Macdonald J**, Porter V, McNamara D. Negative capsule endoscopy in patients with obscure GI bleeding predicts low rebleeding rates. *Gastrointest Endosc* 2008; **68**: 1122-1127 [PMID: 19028220 DOI: 10.1016/j.gie.2008.06.054]
88 **Koh SJ**, Im JP, Kim JW, Kim BG, Lee KL, Kim SG, Kim JS, Jung HC. Long-term outcome in patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *World J Gastroenterol* 2013; **19**: 1632-1638 [PMID: 23539070 DOI: 10.3748/wjg.v19.i10.1632]
89 **Delvaux M**, Fassler I, Gay G. Clinical usefulness of the endoscopic video capsule as the initial intestinal investigation in patients with obscure digestive bleeding: validation of a diagnostic strategy based on the patient outcome after 12 months. *Endoscopy* 2004; **36**: 1067-1073 [PMID: 15578296 DOI: 10.1055/s-2004-826034]
90 **Estévez E**, González-Conde B, Vázquez-Iglesias JL, de Los Angeles Vázquez-Millán M, Pértega S, Alonso PA, Clofent J, Santos E, Ulla JL, Sánchez E. Diagnostic yield and clinical outcomes after capsule endoscopy in 100 consecutive patients with obscure gastrointestinal bleeding. *Eur J Gastroenterol Hepatol* 2006; **18**: 881-888 [PMID: 16825907]

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